

Use of calcium channel blockers in cardiovascular disease

Introduction

Calcium channel blockers (CCBs) are widely used pharmacological agents in the management of cardiovascular disease. They exert their action via selectively blocking cellular entry of calcium through calcium channels on cell membranes and as such, have various therapeutic applications, including the treatment of angina, hypertension and supraventricular arrhythmias (such as atrial fibrillation).

In order to help optimise the use of CCBs in patients for whom they are indicated, it is important that practitioners have a sound understanding of their pharmacological action and role in therapy. This article will briefly describe the action of therapeutically important calcium channels and the mechanism of action of CCBs in cardiovascular disease. A summary of the evidence for the current place in therapy will be provided, along with important practical considerations for their use.

Calcium Channels

Intracellular calcium is required for myocardial and smooth muscle cell contraction, and is also involved in the automaticity of cardiac pacemaker cells (Rang, Dale, Ritter, Flower, & Henderson, 2012). In smooth muscle cells, calcium enters the cytosol through transmembrane calcium channels, whereas in striated muscle cells, calcium is released from intracellular stores by the sarcoplasmic reticulum through ryanodine receptors. In myocardial cells, calcium enters the cell via both mechanisms (figure 1). The transmembrane calcium channels in myocardial, pacemaker and smooth muscle cells are the target of pharmacological intervention in order to regulate intracellular calcium concentrations.

There are a number of known transmembrane calcium channels, of which the voltage-gated L-type calcium channels are therapeutically important. Depolarisation during the action potential activates and opens the voltage-gated L-type calcium channel, resulting in calcium influx. This leads to myosin phosphorylation and muscle

contraction, and the stimulation of ryanodine receptors that further release calcium from the sarcoplasmic reticulum (i.e. calcium-induced calcium release).

Figure 1: *L-type calcium channel blocker function and sites of action of calcium channel blockers.*

Calcium channel blockers block the cellular entry of calcium through L-type calcium channels and in doing so, reduce the concentration of free intracellular calcium (T Godfraind, Miller, & Wibo, 1986). Less available intracellular calcium will reduce the force of contraction in myocardial and vascular smooth muscle cells, and reduce the capacity for spontaneous discharge of pacemaker cells in the sinoatrial (SA) and atrioventricular (AV) nodes. Clinically this will cause vasodilation in resistance and coronary vessels (resulting in a reduction of afterload and increased coronary perfusion, respectively), antidysrhythmic activity, and reduced contractility.

Calcium channel blocker properties

There are three main classes of CCBs in use, determined by their chemical structure: dihydropyridines (DHPs), phenylalkylamines and benzothiazepines (otherwise known as non-dihydropyridines (NDHPs)). Despite their different structures, all CCBs bind close to the channel pore and to the proposed activation gate of the channel's α 1-subunit (Tikhonov & Zhorov, 2009). Upon binding, CCBs interfere with the calcium channel's normal cycle through resting, active and inactive states. This modulation of the gating properties of the channel results in a reduction of calcium concentrations inside the cell.

Calcium channel blockers exhibit distinct patterns of regional potency, with certain drugs preferentially acting on vascular smooth muscle, and others having a greater affinity to myocardial and pacemaker cells in the heart (table 1). Dihydropyridines have preferential affinity for channels that are in an inactive state, such as those in vascular smooth muscle (more so than in cardiac muscle). Non-dihydropyridines favour open and inactive channel states, accessing their binding from inside the cell during channel

opening (Beyl et al., 2006). They stabilise inactive channels, slowing their recovery from inactivation, resulting in frequency dependant inhibition, which increases with heart rate (Hering et al., 1997). As such, DHPs have a potent vasodilating effect without affecting cardiac inotropy at therapeutic doses, whereas NDHPs are more selective for cardiac muscle and can reduce heart rate and contractility (Waller & Sampson, 2017). The main uses for CCBs in clinical practice include the treatment of hypertension, angina and atrial fibrillation; their mechanism of action in these conditions, along with their place in therapy, is outlined below.

Mechanism of action

Hypertension

By decreasing the amount of available intracellular calcium in vascular smooth muscle, CCBs effectively cause smooth muscle relaxation. By dilating arterial resistance vessels (in preference to venous capacitance vessels), CCBs decrease systemic vascular resistance, and arterial blood pressure is reduced. All CCBs work in this way, although the DHPs (e.g. amlodipine, nifedipine) are the most potent vasodilators, and have the greatest affinity to vascular smooth muscle, thus they are the preferential agents in the treatment of hypertension (Lydtin & Trenkwalder, 1990).

Calcium channel blockers are one of the agents used for the initial treatment of hypertension, as recommended by NICE (see table 2). Initial dosing should be low, titrated upwards if necessary in monthly intervals according to response (NICE 2018c). Calcium channel blockers have been shown to be effective in reducing blood pressure, often after the first dose or a few days' treatment (Lydtin & Trenkwalder, 1990; Trenkwalder, 2004).

A recent Cochrane review concluded that when used first-line for hypertension, CCBs prevented stroke and total cardiovascular syndromes, but not coronary heart disease or mortality (Wright, Musini, & Gill, 2018). The evidence was low-quality however, and it is important to consider that CCBs may also increase

the risk of heart failure compared to diuretics, ACE inhibitors and ARBs (Chen et al., 2010).

Angina

The effects of CCBs on blood pressure as outlined above also account for its usefulness in preventing angina pectoris. Lower blood pressure (resulting from a decreased peripheral resistance) results in a decrease in cardiac work of the left ventricle, ventricular afterload, and subsequent myocardial oxygen demand (Theophile Godfraind, 2014). Myocardial oxygen demand is also reduced by the decrease in heart rate and contractility seen with the NDHPs (verapamil and diltiazem). Oxygen supply to the myocardium is improved with the action of CCBs dilating coronary arteries, preventing coronary vasospasm, and improving myocardial blood flow.

Calcium channel blockers, along with beta-blockers, are considered first-line agents for the prevention of angina symptoms (Table 2). Evidence from meta-analyses suggests that CCBs are generally as well-tolerated and effective as beta blockers in reducing angina symptoms (Heidenreich et al., 1999; O'Toole, 2008), but there is a lack of evidence comparing the efficacy of individual CCBs for this purpose. Choice of CCB therefore depends on co-morbidities and concomitant drugs.

For example, NDHPs are contraindicated in heart failure, heart block and bradycardia on account of their negative inotropic and chronotropic properties, which may cause clinical deterioration. For these patients, DHPs would be a safer option (Packer et al., 1996). The addition of DHPs to beta blockers as combination therapy for angina has been shown to be safe and effective in increasing exercise tolerance and duration when monotherapy is insufficient to control symptoms (Klein, Jackson, & Tavazzi, 2002). This is not the case for NDHPs, which should be avoided with beta blockers (see Interactions, below).

Atrial Fibrillation

The AV and SA nodes generate slowly propagating action potentials that are dependent upon the movement of calcium across cell membranes. Calcium channel blockers that have a greater affinity for myocardial pacemaker cells (e.g. NDHPs) reduce the firing rate and conduction velocity at the AV and SA nodes, thereby prolonging repolarisation. This helps to block reentrant mechanisms that can cause supraventricular tachycardias (SVT) (Theophile Godfraind, 2014). The NDHPs are included in the Vaughn Williams classification of antiarrhythmics (class IV) and are used in the management of a variety of arrhythmias, particularly SVTs such as atrial fibrillation (AF), atrial flutter, and paroxysmal SVT.

In AF, rate control with NDHPs has shown to be effective (Ulimoen et al., 2013) and associated with reduced all-cause mortality compared to no rate-control therapy (Chao et al., 2015). They are also associated with improvements in quality of life and exercise tolerance (Fuster et al., 2006). Conclusive data regarding comparative efficacy compared to beta blockers is currently limited, therefore both are currently recommended as first-line agents for rate control, with selection dependant on patient-specific factors such as co-morbidities and contraindications (Table 2).

Precautions for use

Adverse effects

The adverse effects of the DHPs are associated with their vasodilatory properties, and are dose-dependent (Law, Wald, Morris, & Jordan, 2003). For example, dizziness, headache and flushing may commonly occur with first use, but often improve after a few days. Peripheral oedema, particularly in the ankles, can also occur due to the dilatation of pre-capillary arterioles (rather than a result of sodium retention), and thus may be refractory to diuretic treatment (Messerli & Grossman, 2002). Treatment of CCB-induced ankle

oedema may include options such as leg elevation whilst in a supine position, reduction in the dose of CCB, or the addition of an ACE inhibitor (Sica, 2003).

Short-acting DHPs (e.g. nifedipine) can cause excessive hypotension and reflex tachycardia from sympathetic stimulation, and their sudden withdrawal may exacerbate angina. Longer acting DHPs (e.g. amlodipine) are more slowly absorbed from the gastrointestinal tract and are associated with reduced baroreceptor reflex responses (Opie, Yusuf, & Kübler, 2000), and therefore have a more desirable safety profile for hypertension and angina.

The NDHPs can cause excessive bradycardia, heart block and a reduction in contractility, particularly when given intravenously or at high doses. Verapamil commonly causes constipation, and diltiazem has been associated with dermatological reactions (e.g. photosensitivity, rash). The vasodilatory adverse effects described above are less common with the NDHPs and often improve with continued use.

It is important to consider the side-effect profile of individual CCBs when prescribing and administering these drugs, as they may determine their suitability to certain patients. For example, considering the above, patients with unstable angina, bradycardia or heart failure may not be suited to therapy with CCBs, and alternative agents may need to be sought.

Interactions

Calcium channel blockers are metabolised in the liver by cytochrome p450 enzymes, therefore concomitant use of enzyme inducers or inhibitors should be cautioned (Table 3). Patients who have decreased hepatic function should also be monitored for signs of increased plasma CCB concentrations (e.g. heart rate, blood pressure).

One of the notable interactions with CCBs occurs with the HMG-CoA reductase inhibitors atorvastatin and simvastatin. Current recommendations state that if a patient is established on CCB therapy, the lowest possible dose of statin should be used initially, and the dose titrated upwards (NICE 2018a). If a patient

already taking atorvastatin/simvastatin is prescribed a CCB, the statin dose should be lowered and retitrated against serum cholesterol levels. For example, a maximum dose of 20mg simvastatin is currently recommended with the concomitant administration of either amlodipine, verapamil or diltiazem (Joint Formulary Committee, 2018).

Non-dihydropyridine calcium channel blockers (particularly verapamil) depress cardiac function and therefore the concomitant prescription of other cardiodepressants, such as beta blockers, can increase the risk of bradycardia, asystole, severe hypotension or heart failure. As such, verapamil is contraindicated with beta blockers, and the use of diltiazem with beta blockers should be approached with caution (e.g. on specialist advice, with careful monitoring of heart rate and blood pressure).

Conclusion

Calcium channel blockers are widely used, and generally well-tolerated, in the therapy of cardiovascular disease, and are beneficial in the treatment of hypertension, angina and supraventricular tachycardias such as atrial fibrillation. There are important differences between the classes of calcium channel blockers, and their diversity with respect to their selectivity and mechanism of action directs their selection and use in therapy. Caution therefore needs to be exercised when prescribing and administering these drugs in patients prescribed other medications, or who have co-morbidities, in order to confer the maximum benefit of therapy to patients.

Key messages

- Calcium channel blockers act on L-type transmembrane calcium channels to reduce the concentration of intracellular calcium available to promote contraction.
- Clinical uses of calcium channel blockers include the treatment of supraventricular tachycardia, hypertension and the prevention of angina.

- Dihydropyridine calcium channel blockers are mainly used for the treatment of hypertension and prevention of angina, whereas non-dihydropyridine calcium channel blockers are mainly used for dysrhythmias.

CPD Questions

- What are the key differences between the dihydropyridine calcium channel blockers (DHPs) and the non-dihydropyridine calcium channel blockers (NDHPs)?
- Under what circumstances would treatment with NDHP usually be avoided?
- What are the main side effects of DHPs and how are they managed?

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